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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,609	12/12/2003	Jonathan F. Smith	79-02	9335

23713 7590 09/30/2005

GREENLEE WINNER AND SULLIVAN P C
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER

SALVOZA, M FRANCO G

ART UNIT PAPER NUMBER

1648

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/734,609

Applicant(s)

SMITH ET AL.

Examiner

M. Franco Salvoza

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-26, 28-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

Art Unit: 1648

DETAILED ACTION

1. The examiner of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648, Examiner Salvoza.

2. Claims 1, 2, 8, 9, 14, 16, 18-20, 24, 25, 26, 28, 29 and 30 have been amended. Claim 27 has been canceled.

Claim Rejections - 35 U.S.C. § 102(b) **WITHDRAWN**

Claims 17, 24 and 28 were rejected under 35 U.S.C. § 102(b) as being anticipated by Pushko et al. (1997). This rejection is withdrawn in light of applicant's amendments since the reference fails to address the each specific limitation of the claims, including the salt wash step in claim 25 and claim 28.

Claim Rejections – 35 U.S.C. § 103(a) **MAINTAINED**

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 17, 24 and 28 are rejected under 35 U.S.C § 103(a) as being obvious under Pushko et. al. Applicant argues that the Pushko et al. reference does not teach the specific concentrations, and therefore does not teach every limitation of claims 17, 24 and 28 and the rejection should be withdrawn. Applicant argues further that there is no teaching or suggestion

Art Unit: 1648

that particle yield could be or would be improved with the utilization of the particular host cell and nucleic acid concentrations specified in claim 17.

Applicant further points to the specification, which states that “manufacturers’ recommendations are between $1-5 \times 10^6$ cells/ml for Vero and NIH-3T3 cells, and slightly higher for BHK and CHO cells... The art teaches that higher cell densities than those recommended result in non-homogenous field conditions in the electroporation milieu, which can lead to cell fusion.” Applicant also argues that the art teaches the use of “significantly lower cell densities” than those specified in claims 17 and 26.

Applicant’s arguments are considered but found unpersuasive. Pushko et al. does not disclose a specific concentration range, but the concentration limitations are within the reasonably effective concentration parameters of optimization for electroporation mixtures for alphavirus permissive cells in culture medium and concentration of alphavirus RNA replicon vectors that one of ordinary skill in the art would employ. The art teaches a lower range of cell densities but not significantly lower, as argued by applicant. Given the very broad range ($1-5 \times 10^6$ cells/ml) of concentrations, which additionally, are mere “manufacturers’ recommendations,” the range is not significantly lower, rather within the purview of reasonable concentration parameters, especially for optimization. The rejection is maintained.

Applicant also argues that neither the cited reference teaches or suggests that contacting the cells in which viral particles were produced with an aqueous solution of from 0.2 to 5 M ionic strength as specified in step (c) of claim 1 and step (c) of claim 25 could or would improve ARP yield.

Applicant’s arguments are considered but found unpersuasive. Once again, the cited

Art Unit: 1648

range of ionic strength is very broad, and one of ordinary skill in the art would know that such concentrations are within the purview of reasonable concentration parameters for optimization.

The rejection is maintained for reasons of record.

Claims 1, 3-12, 14-26, 28 and 30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pushko et al. in view of Bell et al.

Applicant argues that the combination of the teachings of Pushko et al. and Bell et al. references would not have led one of ordinary skill in the art to the present invention as claimed and argued against the impermissible use of hindsight in evaluating patentability.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant also argues that neither Pushko et al. nor Bell et al. suggests any washing of the virus or particle producing cells in a higher than normal salt solution as a way to improve yield.

Applicant's arguments are considered but found unpersuasive. Pushko et al. teaches production of a modified host cell and culturing to allow expression of at least one helper function to allow replication of the alphaviral replicon nucleic acid and packaging of the nucleic acid to form ARPS, but does not teach the effect of salt concentration. Bell et al. teaches the proliferative effect of increasing salt concentration on the release of alphavirus particles in cell

culture systems on modified host cells, but does not disclose the exact salt concentrations and conditions of the electroporation.

Bell et al. teaches a link between salt concentration and particle release, and one of ordinary skill in the art would be motivated to increase yield and optimize the ranges of the electroporation mix and the gap between the electrodes to enhance transfection. Furthermore, under routine experimentation techniques one would reasonably wash the cell (claim 10 limitation), perform the wash in a medium of reduced salt (claim 12 limitation) and use deoxyribonuclease to remove residual nucleic acid. The range of ionic strength of claim 5 is also within the range of routine optimization and experimentation, and one would reasonably filter or purify the virus per claim 22. Finally, one of ordinary skill in the art would also use capped vs. uncapped transcripts as to claims 13 and 18 as part of routine experimentation and optimization procedures. Ultimately, one of ordinary skill in the art would be motivated to pursue a higher particle yield, and based on the combination of references one would keep the salt concentration higher for a higher particle yield, and Bell et al. shows a reasonable expectation for success in doing so.

Applicant also points to Figure 4 to show that the salt wash can result in as much as a hundred fold increase in ARP yield, and submit that the magnitude of increase in particle yield is significantly greater than one would expect from mere routine optimization of experimental parameters, and that the magnitude increase points to the inventive nature of applicant's discovery of the effect of a high-salt wash on the release of heparin-binding alphaviral particles from the cells in which they are produced.

Applicant's arguments are considered but found unpersuasive. The claims do not recite

the particle yield of virus that is required. Additionally, since Bell et al. teaches that the number of particles is significantly reduced when the salt is lowered, there is no unexpected result between maintaining salt concentration and particle yield. This rejection is maintained for reasons of record.

Claim 2 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Pushko et al. in view of Bell et al. and further in view of Polo et al. Applicant maintains that neither Pushko et al. nor Bell et al. suggests washing with a solution and that a range of ionic strength will neither improve yield nor demonstrate a beneficial effect, and therefore would not meet the limitations of claim 2, drawn to the at least one helper function encoded by nucleic acid stably integrated into the genome of the host cell.

Applicant's arguments are considered but found unpersuasive. As cited above, a combination of Pushko et al and Bell et al. suggest increased yield through salt concentration and a reasonable range of parameters to as part of routine optimization and experimentation techniques. Polo et al. further teach a cell and stable cell lines in which at least one helper function is encoded by nucleic acid and stably integrated within the genome. Therefore, one of ordinary skill in the art would have been motivated to and expected to increase yield using these well-established techniques using stable cell lines to further integrate Polo et al. into the combination of Pushko et al. and Bell et al. references. The rejection is maintained.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


Art Unit: 1648

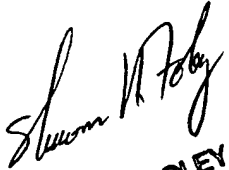
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


M. Franco Salvoza
Patent Examiner


SHANNON FOLEY
PRIMARY EXAMINER